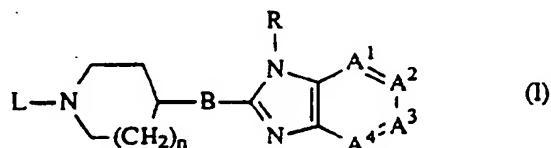




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 513/04, 401/14, 401/04 C07D 519/00, 473/40 A61K 31/505, 31/425 C07D 417/14, 471/04, 473/00 C07D 473/30, A61K 31/52		A1	(11) International Publication Number: WO 92/01697
(21) International Application Number: PCT/EP91/01292		(43) International Publication Date: 6 February 1992 (06.02.92)	
(22) International Filing Date: 9 July 1991 (09.07.91)			
(30) Priority data: 554,325 19 July 1990 (19.07.90) US			
(71) Applicant: JANSSEN PHARMACEUTICA N.V. [BE/ BE]; Turnhoutseweg 30, B-2340 Beerse (BE).		(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN + (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).	
(72) Inventors: JANSSENS, Frans, Eduard ; Tinstraat 79, B- 2820 Bonheiden (BE). SOMMEN, François, Maria ; Langenberg 49, B-2323 Wortel (BE). DIELS, Gaston, Stanislas, Marcella ; Oosteinde 12, B-2380 Ravels (BE).		Published <i>With international search report.</i>	

(54) Title: NOVEL SUBSTITUTED THIAZOLYL AND SUBSTITUTED PYRIDINYL DERIVATIVES



(57) Abstract

Substituted thiazolyl and substituted pyridinyl derivatives of formula (I), the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein -A¹=A₂-A³=A⁴, is a bivalent radical having the formula -CH=CH-CH=CH- (a-1), -N=CH-CH=CH- (a-2), -CH=N-CH=CH- (a-3), -CH=CH-N=CH- (a-4), -CH=CH-CH=N- (a-5), -N=CH-N=CH- (a-6) or -CH=N-CH=N- (a-7); B represents NR¹, CH₂, O, S, SO or SO₂ wherein R¹ is hydrogen or C₁₋₄alkyl; R is a radical of formula (b-1) or (b-2); wherein D is C₁₋₄alkanediyl; R² is C₁₋₆alkyl; n is 0, 1 or 2; L is hydrogen; C₁₋₁₂alkyl; C₃₋₆cycloalkyl; C₃₋₆alkenyl optionally substituted with aryl; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; arylcarbonyl; aryl C₁₋₆alkyloxycarbonyl; or a radical of formula -Alk-R³ (c-1); -Alk-Y-R⁴ (c-2); -Alk-Z¹-C(=X)-Z²-R⁵ (c-3); or -CH₂-CHOH-CH₂-O-R⁶ (c-4); have antiallergic properties. Compositions containing the same and methods of treating warm-blooded animals suffering from allergic diseases.

+ See back of page

+ DESIGNATIONS OF "SU"

It is not yet known for which States of the former Soviet Union any designation of the Soviet Union has effect.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU+	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

5

**NOVEL SUBSTITUTED THIAZOLYL AND SUBSTITUTED
PYRIDINYL DERIVATIVES**

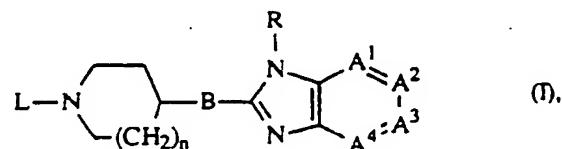
10

Background of the invention

- In US-4,556,660; 4,634,704; 4,695,569; 4,695,575; 4,588,722; 4,835,161; 15 4,897,401 and in EP-A-0,206,415 and 0,297,661 there are disclosed benzimidazole and imidazopyridine substituted piperidine derivatives as antihistaminics and serotonin antagonists.

Description of the invention:

- 20 The present invention is concerned with novel substituted thiazolyl and substituted pyridinyl derivatives having the formula :



- 25 the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

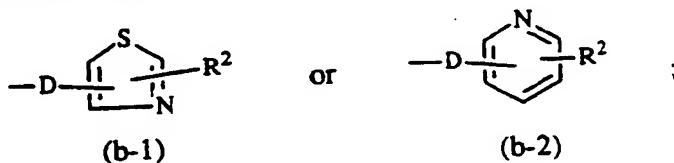
-A¹=A²-A³=A⁴- is a bivalent radical having the formula

- 30 -CH=CH-CH=CH- (a-1),
 -N=CH-CH=CH- (a-2),
 -CH=N-CH=CH- (a-3),
 -CH=CH-N=CH- (a-4),
 -CH=CH-CH=N- (a-5),
 35 -N=CH-N=CH- (a-6) or
 -CH=N-CH=N- (a-7);

2

wherein one or two hydrogen atoms in said radicals (a-1) to (a-7) may each independently be replaced by halo, C₁-6alkyl, C₁-6alkyloxy, hydroxy or trifluoromethyl;

5 B represents NR¹, CH₂, O, S, SO or SO₂ wherein R¹ is hydrogen or C₁₋₄alkyl;
R is a radical of formula;



10 wherein D is C₁₋₄alkanediyl;

R² is C₁₋₆alkyl;

n is 0, 1 or 2;

L is hydrogen; C₁₋₁₂alkyl; C₃₋₆cycloalkyl; C₃₋₆alkenyl optionally substituted with aryl; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; arylcarbonyl; arylC₁₋₆alkyloxy-carbonyl; or a radical of formula

15 carbonyl; or a radical of formula

- Alk-R³ (c-1);
- Alk-Y-R⁴ (c-2);
- Alk-Z¹-C(=X)-Z²-R⁵ (c-3); or
- CH₂-CHOH-CH₂-O-R⁶ (c-4); wherein

R^3 is cyano, aryl or Het;

R⁴ is hydrogen, aryl, Het or C₁₋₆alkyl optionally substituted with aryl or Het;

R⁵ is hydrogen, aryl, Het or C₁-alkyl optionally substituted with aryl or Het;

25 R⁶ is aryl or naphthalenyl;

v is O, S, NR⁷; said R⁷ being hydrogen, C₁₋₆alkyl or C₁₋₆alkylcarbonyl;

Z_1 and Z_2 each independently are O, S, NR⁸ or a direct bond; said R⁸ being

hydrogen or C₁-6 alkyl;

Y is O , S or NR^9 : said R^9 being hydrogen, $\text{C}_1\text{-}\text{6alkyl}$ or cyano;

each Alk independently is C₁-6alkanediyl;

each Het is :

- (i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms selected from oxygen, sulfur and nitrogen, provided that no more than 2 oxygen and/or sulfur atoms are present;

- (ii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring only carbon atoms; or
- (iii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered heterocyclic ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen;
- wherein Het being a monocyclic ring system may be optionally substituted with up to 4 substituents; and wherein Het being a bicyclic ring system may be optionally substituted with up to 6 substituents, said substituents being selected from halo, amino, mono- and di(C₁-6alkyl)amino, arylC₁-6alkylamino, nitro, cyano, aminocarbonyl, C₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio, C₁-6alkyloxycarbonyl, C₁-6alkyloxyC₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, hydroxy, mercapto, hydroxyC₁-6alkyl, C₁-6alkylcarbonyloxy, aryl, arylC₁-6alkyl, carboxyl, C₁-6alkylaminocarbonylamino, arylaminocarbonylamino, oxo or thio;
- each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio, mercapto, amino, mono- and di(C₁-6alkyl)amino, carboxyl, C₁-6alkyloxycarbonyl and C₁-6alkylcarbonyl.
- In the compounds of formula (I) where R³, R⁴ or R⁵ is Het, said Het may be partly or completely saturated, or unsaturated. The compounds of formula (I) wherein Het is partly saturated or unsaturated and is substituted with hydroxy, mercapto or amino, may also exist in their tautomeric forms. Such forms although not explicitly indicated hereinabove, are intended to be included within the scope of the invention.
- As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C₁-4alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methyl-ethyl, butyl, 1,1-dimethylethyl, 1-methylpropyl, 2-methylpropyl; C₁-6alkyl defines C₁-4alkyl radicals as defined hereinabove and the higher homologs thereof having 5 or 6 carbon atoms; C₁-12alkyl defines C₁-4alkyl radicals as defined hereinabove and the higher homologs thereof having from 5 to 12 carbon atoms; C₃-6cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; C₃-6alkenyl defines straight and

branch chained hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 3-but enyl, 2-but enyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-but enyl and the like; and when a C₃-alkenyl is substituted on a heteroatom, then the carbon atom of said C₃-alkenyl connected to said heteroatom preferably is saturated; C₁₋₄alkanediyl defines bivalent straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the branched isomers thereof; C₁₋₆alkanediyl defines C₁₋₄alkanediyl radicals as defined hereinabove and the higher homologs thereof having 5 or 6 carbon atoms such as, for example, 1,5-pentane-10 diyl, 1,6-hexanediyl and the branched isomers thereof.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. Said salt forms can conveniently be obtained by treating the base form of the compounds of formula (I) with appropriate acids such as inorganic acids, for example, hydrohalic acid, e.g. hydrochloric, hydrobromic and the like acids, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 20 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

25 The term acid addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The compounds of this invention may have several asymmetric carbon atoms in their structure. Each of these chiral centers may be indicated by the stereochemical descriptors R and S.

30 Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like; and enantiomers may be separated from each other following art-known resolution methods, for example, by the selective crystallization of their diastereomeric salts with chiral

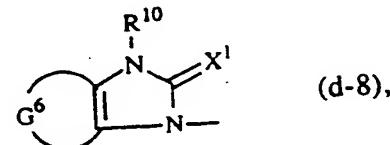
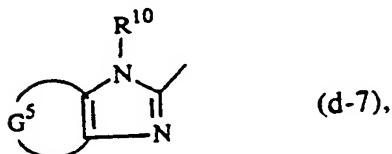
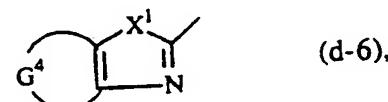
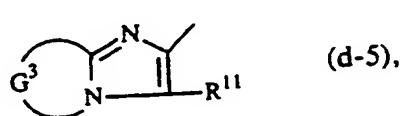
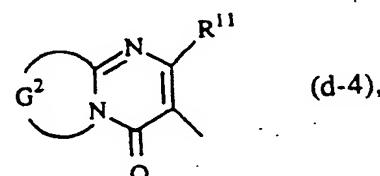
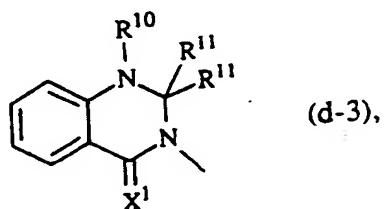
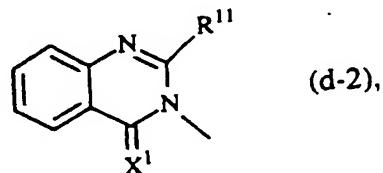
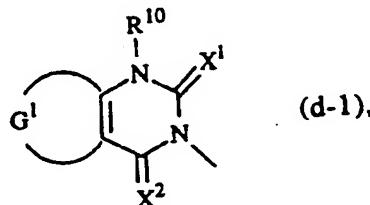
acids. Pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reactions occur stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereoselective methods of preparation. These methods will advantageously employ enantiomerically pure starting materials. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be included within the scope of the invention.

In particular, the radical Het as defined hereinabove may be selected from pyridinyl, 10 optionally substituted with one or two substituents each independently selected from halo, amino, mono- and di(C₁-6alkyl)amino, arylC₁-6alkylamino, nitro, cyano, amino-carbonyl, C₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio, C₁-6alkyloxycarbonyl, hydroxy, C₁-6alkylcarbonyloxy, arylC₁-6alkyl and carboxyl; pyridinyloxide, optionally substituted with nitro; pyrimidinyl, optionally substituted with one or two substituents each 15 independently selected from halo, amino, C₁-6alkylamino, arylC₁-6alkylamino, hydroxy, C₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio and arylC₁-6alkyl; pyridazinyl, optionally substituted with C₁-6alkyl or halo; pyrazinyl, optionally substituted with halo, amino or C₁-6alkyl; thienyl, optionally substituted with halo or C₁-6alkyl; furanyl, 20 optionally substituted with halo or C₁-6alkyl; pyrrolyl, optionally substituted with C₁-6alkyl; thiazolyl, optionally substituted with C₁-6alkyl, C₁-6alkyloxycarbonyl, aryl or arylC₁-6alkyl; imidazolyl, optionally substituted with one or two substituents each independently selected from C₁-6alkyl, arylC₁-6alkyl and nitro; tetrazolyl, optionally substituted with C₁-6alkyl; 1,3,4-thiadiazolyl, optionally substituted with C₁-6alkyl or amino; 5,6-dihydro-4H-1,3-thiazin-2-yl, optionally substituted with C₁-6alkyl; 4,5-di- 25 hydrothiazolyl, optionally substituted with C₁-6alkyl; oxazolyl, optionally substituted with C₁-6alkyl; 4,5-dihydro-5-oxo-1H-tetrazolyl, optionally substituted with C₁-6alkyl; 1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl, optionally substituted with C₁-6alkyl; 3,4-dihydro-4-oxopyrimidinyl or 4,5-dihydro-4-oxopyrimidinyl, both radicals 30 optionally substituted with up to 3 substituents selected from C₁-6alkyl, amino, C₁-6alkylaminocarbonylamino, arylaminocarbonylamino, arylC₁-6alkylamino and C₁-6alkylamino; 2,3-dihydro-3-oxopyridazinyl; 2-oxo-3-oxazolidinyl; pyrrolidinyl; piperidinyl; morpholinyl; thiomorpholinyl; dioxanyl, optionally substituted with C₁-6alkyl; indolyl, optionally substituted with hydroxy or C₁-6alkyl; quinolinyl, 35 optionally substituted with hydroxy or C₁-6alkyl; quinoxalinyl, optionally substituted with C₁-6alkyl; phthalazinyl, optionally substituted with halo; 1,3-dioxo-1H-isoindol-2(3H)-yl; 2,3-dihydro-3-oxo-4H-benzoxazinyl and 2,3-dihydro-1,4-benzodioxinyl, both being optionally

6

substituted with C₁-alkyl or halo; 2-oxo-2H-1-benzopyranyl and 4-oxo-4H-1-benzo-pyranyl, both being optionally substituted with C₁-alkyl; 3,7-dihydro-1,3-dimethyl-2,6-dioxo-1H-purin-7-yl, optionally substituted with C₁-alkyl; 6-purinyl, and

5 a bicyclic heterocyclic radical of formula



10

wherein

X¹ and X² each independently are O or S;

each R¹⁰ independently is hydrogen, C₁-alkyl, arylC₁-alkyl, C₁-alkyloxy-C₁-alkyl, hydroxyC₁-alkyl or C₁-alkyloxycarbonyl;

each R¹¹ independently is hydrogen, C₁-alkyl, hydroxy, mercapto, C₁-alkyloxy, C₁-alkylthio, halo or C₁-alkyloxycarbonylC₁-alkyl;

15 each R¹¹ independently is hydrogen, C₁-alkyl, hydroxy, mercapto, C₁-alkyloxy, C₁-alkylthio, halo or C₁-alkyloxycarbonylC₁-alkyl;

G¹ is -CH=CH-CH=CH-; -S-CH=CH- or -N=CH-NH-;

G² is -CH=CH-CH=CH-, -(CH₂)₄-, -S-(CH₂)₂-, -S-(CH₂)₃-, -S-CH=CH-, -CH=CH-O-, -NH-(CH₂)₂-, -NH-(CH₂)₃-, -NH-CH=CH-, -NH-N=CH-CH₂-, -NH-CH=N- or -NH-N=CH-;

20

G^3 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{NH}-(\text{CH}_2)_2-$, $-\text{S}-\text{CH}=\text{CH}-$, $-\text{S}-(\text{CH}_2)_3-$,
 $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$,
 $-\text{N}=\text{CH}-\text{N}=\text{CH}-$ or $-\text{CH}=\text{N}-\text{CH}=\text{N}-$;

G^4 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{NH}-(\text{CH}_2)_2-$, $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$,
5 $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$, $-\text{N}=\text{CH}-\text{N}=\text{CH}-$ or
 $-\text{CH}=\text{N}-\text{CH}=\text{N}-$;

G^5 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$,
 $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$, $-\text{N}=\text{CH}-\text{N}=\text{CH}-$ or $-\text{CH}=\text{N}-\text{CH}=\text{N}-$;

G^6 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$,
10 $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$, $-\text{N}=\text{CH}-\text{N}=\text{CH}-$ or $-\text{CH}=\text{N}-\text{CH}=\text{N}-$;

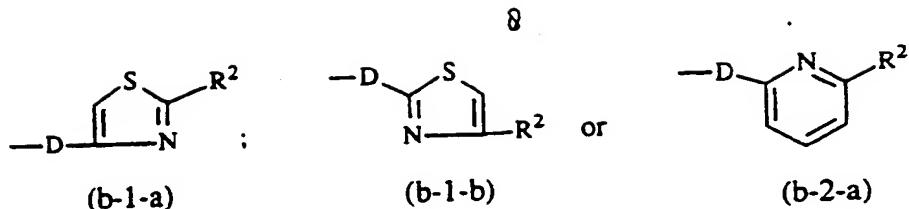
wherein one or two hydrogen atoms in the benzene part of the radicals of formula (d-2) or (d-3) or one or two hydrogen atoms in said radicals G^1 , G^2 , G^3 , G^4 , G^5 or
15 G^6 may be replaced by C_{1-6} alkyl, C_{1-6} alkylothio, C_{1-6} alkyloxy or halo, when connected to a carbon atom; or by C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl or aryl C_{1-6} alkyl when connected to a nitrogen atom; and aryl is as defined hereinabove.

Aryl as used in the definition of R^3 , R^4 and R^5 , in particular is phenyl optionally substituted with halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkyloxy; aryl as used in the
20 definition of R^6 in particular is phenyl optionally substituted with halo.

A particular subgroup among the compounds of formula (I) comprises those compounds of formula (I) wherein $-A^1-A^2-A^3-A^4-$ is a bivalent radical of formula (a-1) or (a-2); another particular subgroup among the compounds of formula (I)
25 comprises those compounds of formula (I) wherein $-A^1-A^2-A^3-A^4-$ is a bivalent radical having a formula (a-3) through (a-5); wherein one or two hydrogen atoms in said radicals (a-1) to (a-5) may each independently be replaced by C_{1-6} alkyloxy or hydroxy.

Particularly interesting compounds are those compounds of any of the former groups or subgroups wherein B is NR^2 , O or CH_2 ; and/or L is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl, or a radical of formula (c-1), (c-2), (c-3) or (c-4).

More particularly interesting compounds are those particularly interesting
30 compounds of formula (I) wherein B is NH or CH_2 ; and/or n is 1 or 2; and/or R is a radical of formula :



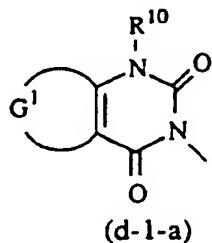
- Preferred compounds are any of the above defined groups of compounds wherein -A¹=A²-A³=A⁴- is a bivalent radical of formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2); wherein one or two hydrogen atoms in said radicals (a-1) or (a-2) may each independently be replaced by C₁-C₆alkyloxy or hydroxy; D is CH₂; and/or L is hydrogen; C₁-C₆alkyl; a radical of formula (c-1) wherein R³ is aryl or Het; a radical of formula (c-2) wherein Y is NH or O and R⁴ is aryl or Het; or a radical of formula -Alk-NH-CO-Het (c-3-a); wherein each Het is pyridinyl, optionally substituted with amino or C₁-C₆alkyl; pyrimidinyl, optionally substituted with amino or C₁-C₆alkyl; pyrazinyl, optionally substituted with amino; thienyl; furanyl; thiazolyl, optionally substituted with C₁-C₆alkyl; imidazolyl, optionally substituted with C₁-C₆alkyl; tetrazolyl, optionally substituted with C₁-C₆alkyl; 1,3,4-thiadiazolyl, optionally substituted with C₁-C₆alkyl or amino; oxazolyl, optionally substituted with C₁-C₆alkyl; 4,5-dihydro-5-oxo-C₁-C₆alkyl, optionally substituted with C₁-C₆alkyl; 1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl; 3,4-dihydro-4-oxopyrimidinyl, optionally substituted with up to 3 substituents selected from C₁-C₆alkyl, amino and C₁-C₆alkylamino; 2-oxo-3-oxazolidinyl; indolyl, optionally substituted with C₁-C₆alkyl; phthalazinyl; 2-oxo-2H-1-benzopyranyl; 3,7-dihydro-1,3-dimethyl-2,6-dioxo-1H-purin-7-yl, optionally substituted with C₁-C₆alkyl; 6-purinyl, or a bicyclic heterocyclic radical of formula (d-1) to (d-8) as defined hereinabove, wherein R¹⁰ and R¹¹ each independently are hydrogen or C₁-C₆alkyl and in the radicals (d-2) and (d-3), X¹ is O, and;
- each aryl is unsubstituted phenyl; phenyl substituted with 1 or 2 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl,
- C₁-C₆alkyl and C₁-C₆alkyloxy; and optionally further substituted with a third substituent selected from halo, C₁-C₆alkyl or C₁-C₆alkyloxy.

More preferred compounds are those preferred compounds wherein L is hydrogen or C₁-C₃alkyl.

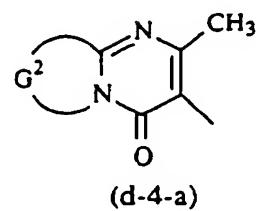
- Further more preferred compounds are those preferred compounds wherein L is a radical of formula -Alk-R³ (c-1) wherein R³ is 4-methoxyphenyl; 4-hydroxyphenyl; thienyl; thiazolyl optionally substituted with C₁-C₆alkyl; oxazolyl; 4,5-dihydro-1H-tetrazolyl optionally substituted with C₁-C₆alkyl; 2,3-dihydro-2-oxo-benzimidazol-1-yl;

9

1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl; thienyl; 2-oxo-2H-1-benzopyranyl or R³ is a radical of formula



or



5

wherein G¹, G² and R¹⁰ are as defined hereinabove.

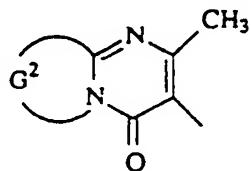
- Still other more preferred compounds are those preferred compounds wherein L is a radical of formula -Alk-Y-R⁴ (c-2) wherein Y is NH or O and R⁴ is thiazolyl, pyridinyl, 1,3,4-thiadiazolyl optionally substituted with C₁₋₆alkyl or amino, pyrimidinyl optionally substituted with amino, 6-purinyl, 3,4-dihydro-4-oxopyrimidinyl, phthalazinyl or 3H-imidazo[4,5-c]pyridin-2-yl.
- 10 1,3,4-thiadiazolyl optionally substituted with C₁₋₆alkyl or amino, pyrimidinyl optionally substituted with amino, 6-purinyl, 3,4-dihydro-4-oxopyrimidinyl, phthalazinyl or 3H-imidazo[4,5-c]pyridin-2-yl.

- Interesting compounds within the present invention are those compounds of formula (I) wherein -A¹=A²-A³=A⁴- represents a bivalent radical of formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2); B represents NH, CH₂ or O; R represents a radical of formula
- 15 (b-1-c) (b-1-d) (b-1-e) or (b-2-b)

20

R² represents C₁₋₄alkyl; n is 1; L represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyl-oxy carbonyl or a radical of formula -Alk-R³ (c-1), -Alk-Y-R⁴ (c-2) or -Alk-Z¹-C(=X)-Z²-R⁵ (c-3); Alk represents C₁₋₄alkanediyl; R³ represents phenyl, C₁₋₄alkyloxyphenyl or a radical of formula

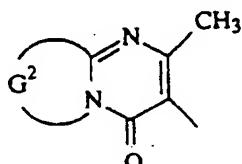
25



10

wherein G² represents -CH=CH-CH=CH-, -S-(CH₂)₃-, -S-(CH₂)₂- or -S-CH=CH-; Y represents O or NH; R⁴ represents hydrogen, C₁₋₄alkyl or pyrimidinyl; R⁵ represents C₁₋₄alkyl; Z¹ represents NH; Z² represents O; and X represents O.

- 5 Particularly interesting compounds are those interesting compounds wherein B represents NH or CH₂; R² represents methyl; L represents C₁₋₄alkyl or a radical of formula -Alk-R³ (c-1), -Alk-Y-R⁴ (c-2) or -Alk-Z¹-C(=X)-Z²-R⁵ (c-3); Alk represents C₂₋₄alkanediyl; R³ represents 4-methoxyphenyl or a radical of formula

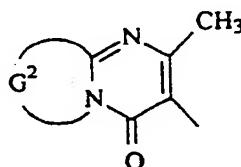


10

wherein G² represents CH=CH-CH=CH-, -S-(CH₂)₃-, -S-(CH₂)₂- or -S-CH=CH-; Y represents O or NH; and R⁴ represents C₁₋₄alkyl or 2-pyrimidinyl.

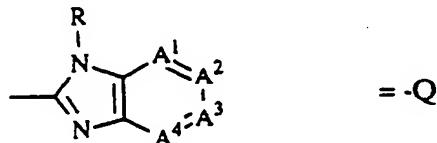
- 15 Other particularly interesting compounds are those interesting compounds wherein B represents NH or CH₂; R² represents methyl; L represents hydrogen, C₁₋₄alkyloxy-carbonyl, phenylmethyl, hydroxyethyl or aminoethyl.

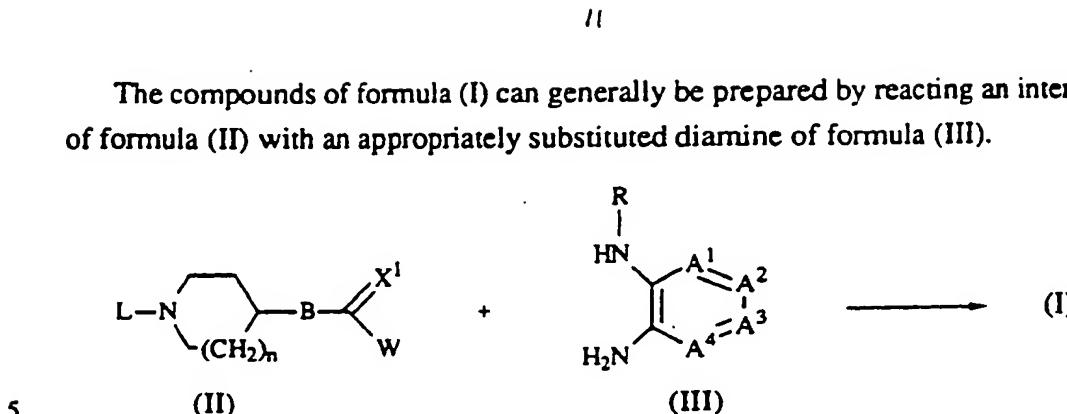
- 20 Especially interesting compounds are those particularly interesting compounds wherein L represents methyl or a radical of formula -Alk-R³ (c-1), Alk represents 1,2-ethanediyl and R³ represents 4-methoxyphenyl or a radical of formula



- 25 wherein G² represents -CH=CH-CH=CH-, -S-(CH₂)₃-, -S-(CH₂)₂- or -S-CH=CH-.

- In order to simplify the structural representation of some of the compounds and intermediates in the following preparations the moiety containing the imidazole group fused to a benzene, pyridine or pyrimidine ring will hereinafter be represented by the symbol Q.

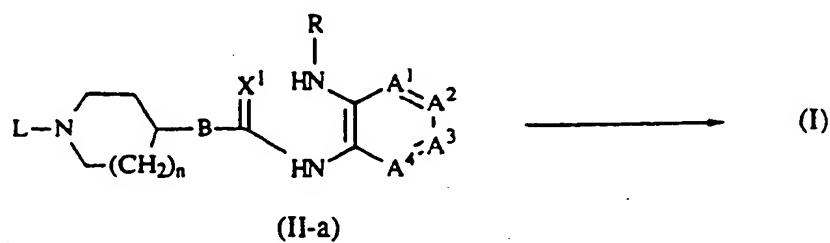




In this and the following reaction schemes W represents an appropriate reactive leaving group such as, for example, halo, e.g. chloro, bromo or iodo; C₁-alkyloxy; C₁-alkylthio, aryloxy or arylthio; and X¹ denotes O, S or NH.

- 10 The derivatives of formula (II) wherein B is CH_2 and W is halo may be generated in situ, for example, by halogenating the corresponding carboxylic acid with thionyl chloride, phosphorous trichloride, phosphoryl chloride, polyphosphoric acid and the like reagents. The reaction of (II) with (III) may be conducted in a suitable reaction-inert solvent such as, for example, a hydrocarbon, e.g., benzene, hexane and the like; an ether, e.g., 1,1'-oxybisethane, tetrahydrofuran and the like; a ketone, e.g., 2-propanone, 2-butanone and the like; an alcohol, e.g., methanol, ethanol, 2-propanol, 1-butanol and the like; a halogenated hydrocarbon, e.g., trichloromethane, dichloromethane and the like; an organic acid, e.g., acetic acid, propanoic acid and the like; a dipolar aprotic solvent e.g., N,N-dimethylformamide, N,N-dimethylacetamide and the like; or a mixture of such solvents. Depending upon the nature of the solvent and W it may be appropriate to add to the reaction mixture a base such as is commonly employed in the art of conducting N-alkylation reactions and/or a iodide salt such as an alkali metal iodide. Elevated temperatures and stirring may enhance the reaction rate.

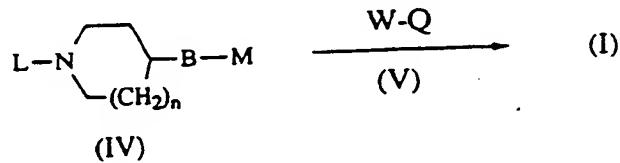
In some instances the reaction of (II) with (III) may first yield an intermediate of formula (II-a) which subsequently may be cyclized to the desired compound of formula (I), either *in situ* or, if desired, after isolation and purification.



12

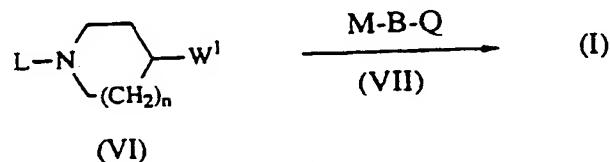
The compounds of formula (I) can also be prepared by reacting an intermediate of formula (IV) with an intermediate of formula (V) following art-known substitution reaction procedures. In (IV) and hereinafter, M is hydrogen when B is other than CH₂, or M represents an alkali or earth alkaline metal such as, for example, lithium or magnesium, when B represents CH₂.

5



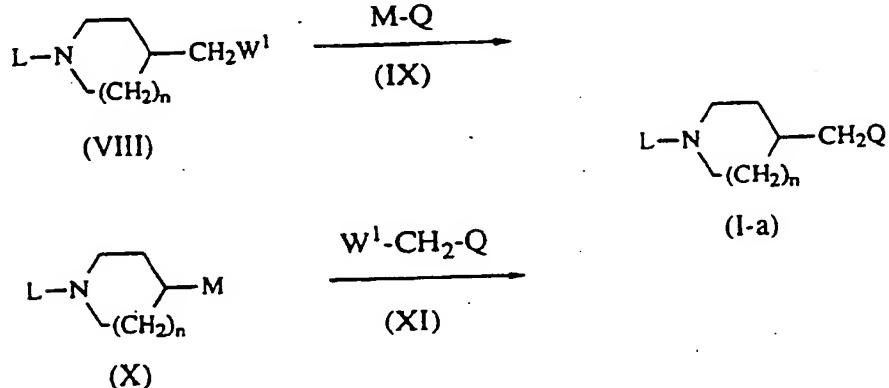
Similarly, the compounds of formula (I) can also be prepared by reacting an intermediate of formula (VI) with an intermediate of formula (VII) wherein M has the previously defined meaning. In formula (VI) and hereinafter W¹ represents an appropriate leaving group such as, for example, halo, e.g., chloro, bromo and the like; or a sulfonyloxy group such as, for example, methanesulfonyloxy, 4-methylbenzene-sulfonyloxy and the like.

15



The compounds of formula (I) wherein B is -CH₂-, said compounds being represented by formula (I-a), can also be prepared by reacting an intermediate of formula (VIII) with an intermediate of formula (IX) or alternatively, by reacting an intermediate of formula (X) with an intermediate of formula (XI).

20



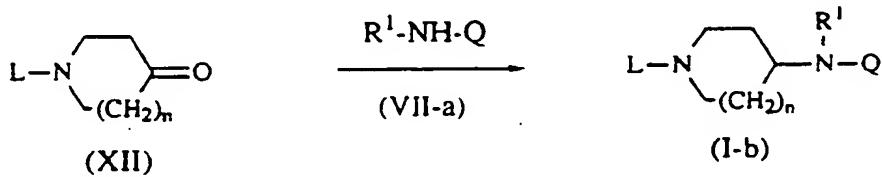
25 The reactions of (IV), (VI), (VIII) and (X) with respectively (V), (VII), (IX) and (XI) may conveniently be conducted in an appropriate reaction-inert solvent such as for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene and the like; an ether,

13

- e.g. 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran and the like; a halogenated hydrocarbon, e.g. trichloromethane and the like; N,N-dimethylformamide; N,N-dimethylacetamide; nitrobenzene; dimethylsulfoxide; 1-methyl-2-pyrrolidinone and the like; and when M is hydrogen, said solvent may also be a C₁-6alkanol, e.g., methanol, 5 ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like. In some instances, particularly when B is a heteroatom, the addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, e.g., sodium carbonate, sodium hydrogen carbonate and the like; sodium hydride; or an organic base such as, for example, N,N-diethylethanamine or N-(1-methylethyl)-10 2-propanamine and/or the addition of an iodide salt, preferably an alkali metal iodide, may be appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction. A convenient alternative for reacting the intermediate of formula (IV) wherein -B-M represents -NH₂ with the reagents of formula (V) comprises stirring and heating the reactants in the presence of copper metal in a reaction-inert solvent such as 15 described hereinbefore, in particular a dipolar aprotic solvent, e.g. N,N-dimethyl-formamide, N,N-dimethylacetamide and the like.

The compounds of formula (I) wherein B is $-NR^1-$, said compounds being represented by formula (I-b), can also be prepared by reacting an intermediate of

- 20 formula (XII) with an intermediate of formula (VII) wherein B-M represents a radical -NR¹-H, said intermediate being represented by formula (VII-a), following art-known reductive N-alkylation procedures.



- 25 The reaction of (XII) with (VII-a) can conveniently be carried out by mixing the reactants in a suitable reaction-inert solvent with an appropriate reductant. Preferably, the ketone of formula (XII) is first reacted with the intermediate of formula (VII-a) to form an enamine, which optionally may be isolated and further purified, and subsequently reducing said enamine. Suitable solvents are, for example, water,
30 C₁-6alkanols, e.g., methanol, ethanol, 2-propanol and the like; ethers, e.g., 1,4-dioxane and the like; halogenated hydrocarbons, e.g., trichloromethane and the like; dipolar aprotic solvents, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide and the like; or a mixture of such solvents. Appropriate reductants are for example, metal or complex metal hydrides, e.g., sodium borohydride, sodium
35 cyanoborohydride, lithium aluminum hydride and the like. Alternatively, hydrogen in

the presence of a suitable catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal and the like may be used as reductant. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products it may be advantageous to add an appropriate catalyst poison to the reaction mixture such as, for example, thiophene and the like.

5

The compounds of formula (I-b) wherein R¹ is H, said compounds being represented by formula (I-b-1), can also be prepared by a cyclodesulfurization reaction of an appropriate thiourea of formula (II-a) wherein X¹ is S, said thiourea being represented by formula (II-a-1), which may be formed in situ by condensing an isothiocyanate of formula (XIII) with a diamine of formula (III).

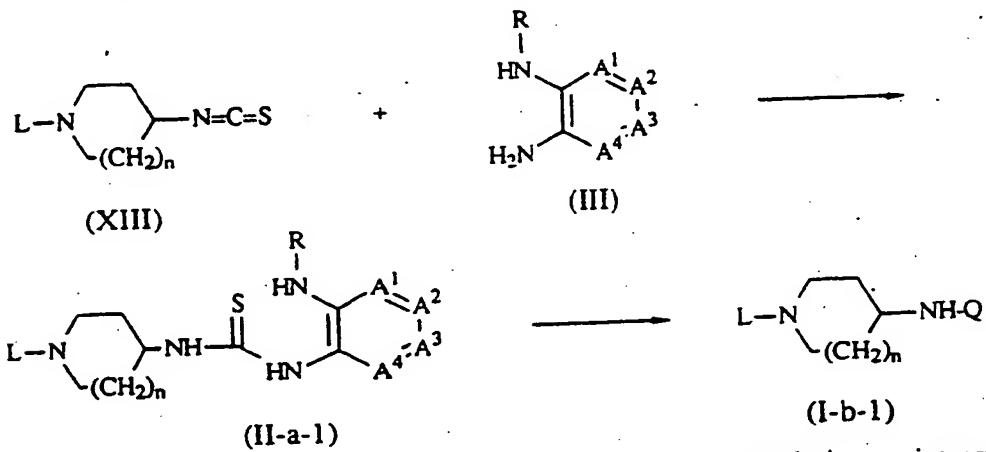
10

Said cyclodesulfurization reaction may be carried out by reacting (II-a-1) with an appropriate alkyl halide, preferably iodomethane, in a suitable reaction-inert organic solvent such as a C₁-6alkanol, e.g., methanol, ethanol, 2-propanol and the like.

15

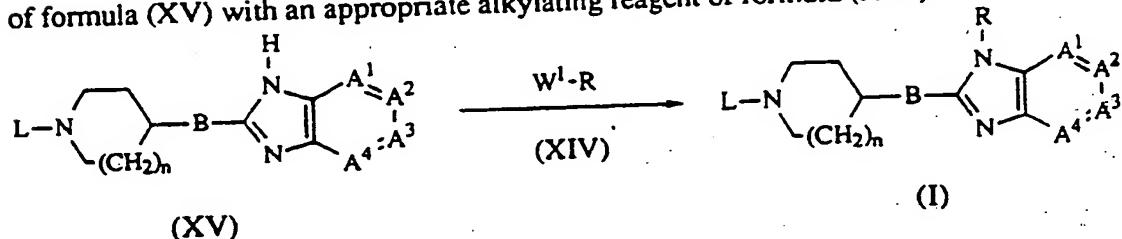
Alternatively, said cyclodesulfurization reaction may also be carried out by the reaction of (II-a-1) with an appropriate metal oxide or salt such as, for example, a Hg(II) or Pb(II) oxide or salt, e.g., HgO, HgCl₂, Hg(OAc)₂, PbO or Pb(OAc)₂ in an appropriate solvent following art-known procedures. In some instances it may be appropriate to supplement the reaction mixture with a small amount of sulfur. Also methanediimides, especially dicyclohexylcarbodiimide may be used as cyclodesulfurizing agents.

20



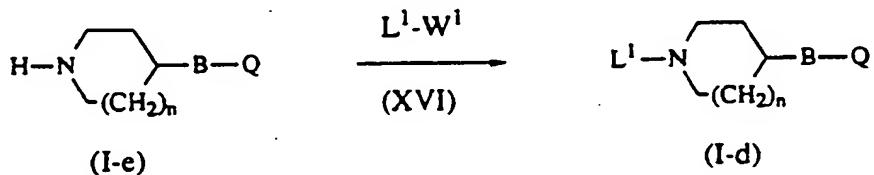
The compounds of formula (I) can also be prepared by N-alkylating an intermediate of formula (XV) with an appropriate alkylating reagent of formula (XIV).

25



- Said N-alkylation reaction can conveniently be conducted in a reaction-inert solvent such as, for example, water; an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; an alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., tetrahydrofuran, 1,4-dioxane, 1,1'-oxybisethane and the like; a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, nitrobenzene, 1-methyl-2-pyrrolidinone and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, potassium tert. butoxide, sodium hydride, sodium amide, sodium hydroxide, calcium carbonate, calcium hydroxide, calcium oxide and the like; or an organic base, such as, for example, an amine, e.g., N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, pyridine and the like may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction. Additionally, it may be advantageous to conduct said N-alkylation under an inert atmosphere such as, for example, oxygen-free argon or nitrogen.
- Alternatively, said N-alkylation may be carried out by applying art-known conditions of phase transfer catalysis reactions. Said conditions comprise stirring the reactants with an appropriate base and optionally under an inert atmosphere as described hereinabove, in the presence of a suitable phase transfer catalyst such as, for example, a trialkylphenylimethylammonium, tetraalkylammonium, tetraalkylphosphonium, tetraarylphosphonium halide, hydroxide, hydrogen sulfate and the like catalysts.

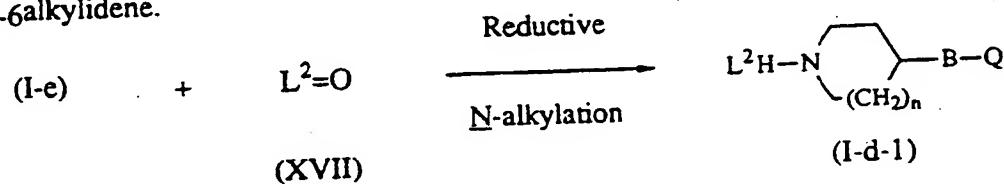
The compounds of formula (I) wherein L is other than hydrogen, said L being represented by L^1 , and said compounds being represented by formula (I-d) can also be prepared by N-alkylating a compound of formula (I) wherein L is hydrogen, said compound being represented by (I-e), with an alkylating reagent of formula (XVI).



16

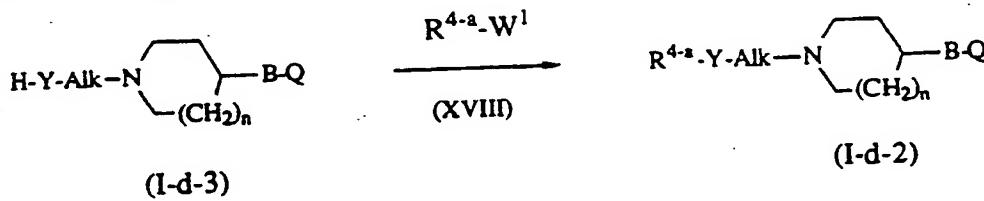
Said N-alkylation is conveniently conducted following art-known N-alkylation procedures as described hereinabove for the preparation of (I) from (XIV) and (XV).

- The compounds of formula (I-d) wherein L is C₃-6cycloalkyl, C₁-12alkyl, a radical of formula (c-1), (c-2) or (c-3), said radicals being represented by the radical L²H- and said compounds by formula (I-d-1) can also be prepared by the reductive N-alkylation reaction of (I-e) with an appropriate ketone or aldehyde of formula L²=O (XVII), said L²=O being an intermediate of formula L²H₂ wherein two geminal hydrogen atoms are replaced by =O, and L² is a geminal bivalent radical comprising C₃-6cycloalkylidene, C₁-12alkylidene, R³-C₁-6alkylidene, R⁴-Y-C₁-6alkylidene and R⁵-Z²-C(=X)-Z¹-C₁-6alkylidene.

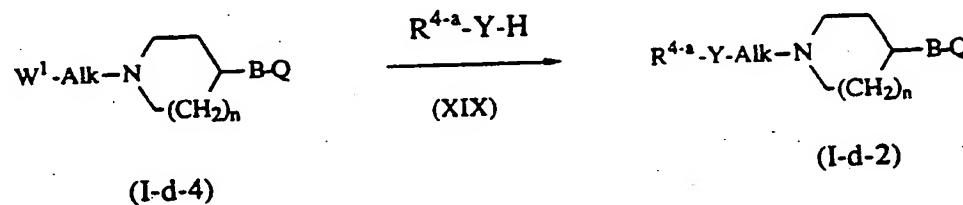


- Said reductive N-alkylation can conveniently be carried out following the procedures described hereinabove for the preparation of compounds of formula (I-b) from (VII-a) and (XII), more particularly following the catalytic hydrogenation procedures.

- The compounds of formula (I) wherein L is a radical of formula (c-2) and R⁴ is aryl or Het, said R⁴ being represented by R^{4-a} and said compounds by formula (I-d-2) may also be prepared by alkylating a compound of formula (I) wherein L is a radical of formula (c-2) and R⁴ is hydrogen, said compounds being represented by formula (I-d-3), with a reagent of formula (XVIII).

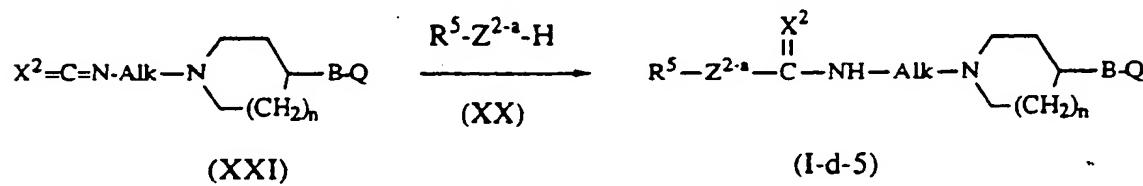


- Similarly, the compounds of formula (I-d-2) may also be prepared by treating a compound of formula (I-d-4) with a reagent of formula (XIX).

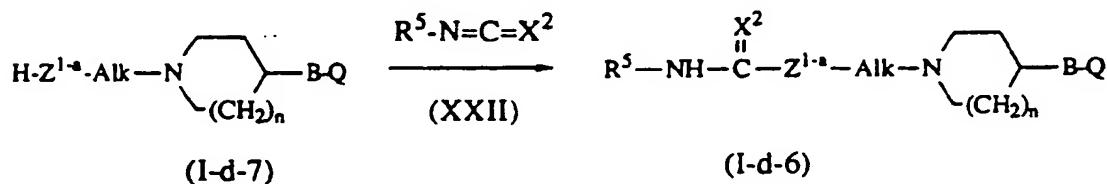


- The alkylation reactions of (I-d-3) with (XVIII) and (I-d-4) with (XIX) may conveniently be conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene; a ketone, e.g.,
- 5 2-propanone, 4-methyl-2-pentanone; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran; and a dipolar aprotic solvent, e.g., N,N-dimethylformamide; N,N-dimethylacetamide; dimethyl sulfoxide; nitrobenzene; 1-methyl-2-pyrrolidinone; and the like. The addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, sodium hydride or an organic base such as, for example,
- 10 N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be utilized to pick up the acid which is liberated during the course of the reaction. Somewhat elevated temperatures may enhance the rate of the reaction.

The compounds of formula (I) wherein L is a radical of formula (c-3), Z¹ is NH, Z² is other than a direct bond and X is other than NR⁹, said Z² and X being represented by Z^{2-a} and X², and said compounds by (I-d-5), can be prepared by reacting an isocyanate (X² = O) or isothiocyanate (X² = S) of formula (XXI) with a reagent of formula (XX).



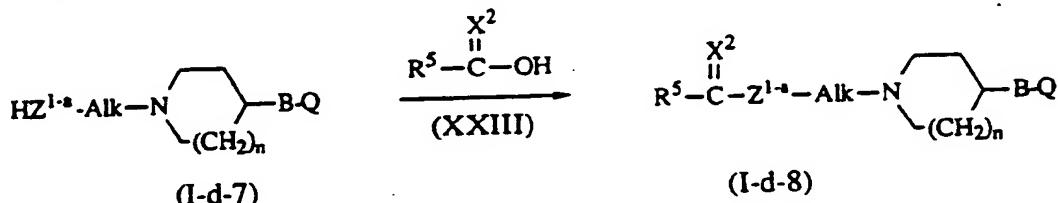
The compounds of formula (I) wherein L is a radical of formula (c-3), Z² is NH, Z¹ is other than a direct bond and X is other than NR⁹, said Z¹ and X being represented by Z^{1-a} and X², and said compounds by (I-d-6), can be prepared by reacting an isocyanate (X² = O) or isothiocyanate (X² = S) of formula (XXII) with a compound of formula (I-d-7).



The reaction of (XX) with (XXI), or (XXII) with (I-d-7) can generally be conducted in a suitable reaction-inert solvent such as, for example, an ether, e.g., tetrahydrofuran and the like, a halogenated hydrocarbon, e.g., trichloromethane and the like. Elevated temperatures may be suitable to enhance the rate of the reaction.

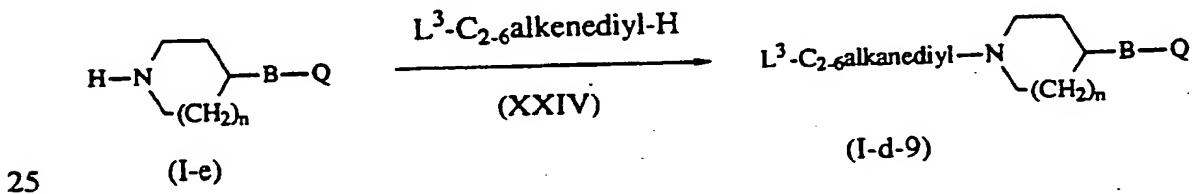
18

The compounds of formula (I) wherein L is a radical of formula (c-3), Z^2 is a direct bond, Z^1 is other than a direct bond and X is other than NR^9 , said Z^1 and X being represented by Z^{1-a} and X^2 , said compounds being represented by (I-d-8), can be prepared by reacting a reagent of formula (XXIII) or a reactive functional derivative thereof with a compound of formula (I-d-7).



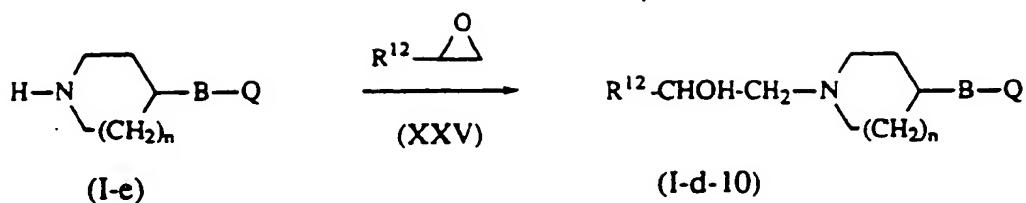
The reaction of (XXIII) with (I-d-7) may generally be conducted following art-known esterification or amidation reaction procedures. For example, the carboxylic acid may be converted into a reactive derivative, e.g., an anhydride or a carboxylic acid halide, which subsequently is reacted with (I-d-7); or by reacting (XXIII) and (I-d-7) with a suitable reagent capable of forming amides or esters, e.g., N,N-methanetetrabisis[cyclohexamine], 2-chloro-1-methylpyridinium iodide and the like. Said reactions may most conveniently be conducted in a suitable solvent such as, for example, an ether, e.g., tetrahydrofuran, a halogenated hydrocarbon, e.g., dichloromethane, trichloromethane, a dipolar aprotic solvent and the like. The addition of a base such as, for example, N,N-diethylethanamine and the like may be appropriate.

20 The compounds of formula (I) wherein L is a radical of formula $L^3\text{-C}_2\text{-6alkanediyl}$,
 said L^3 being aryl, Het or a radical of formula $R^5\text{-Z}^2\text{-C}(=X)\text{-}$, and said compounds
 being represented by formula (I-d-9), may also be prepared by the addition reaction of a
 compound of formula (I-e) to an appropriate alkene of formula (XXIV).



The compounds of formula (I) wherein L is 2-hydroxy-C₂-alkyl or a radical of formula (c-4), said compounds being represented by formula (I-d-10), can be prepared by reacting a compound of formula (I-e) with an epoxide (XXV) wherein R¹² is hydrogen, C₁₋₄alkyl or a radical R⁶-O-CH₂-.

19



The reaction of (I-e) with respectively (XXIV) and (XXV) may be conducted by stirring and, if desired, heating the reactants in a reaction-inert solvent such as, for

- 5 example, a ketone, e.g., 2-propanone, 4-methyl-2-pentanone, an ether, e.g., tetrahydrofuran, 1,1'-oxybisethane, an alcohol, e.g., methanol, ethanol, 1-butanol, a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, and the like.

- 10 The compounds of formula (I) wherein R³, R⁴ or R⁵ are Het, may also be prepared following art-known procedures for preparing heterocyclic ring systems or following analogous methods. A number of such cyclization procedures are described in for example, US-4,695,575 and in the references cited therein, in particular US-4,335,127; 4,342,870 and 4,443,451.

- 15 The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation. Some examples of such procedures are cited hereinafter. The compounds of formula (I) containing a cyano substituent can be converted into the corresponding amines by stirring and, if desired,
- 20 heating the starting cyano compounds in a hydrogen containing medium in the presence of an appropriate catalyst such as, for example, platinum-on-charcoal, Raney-nickel and the like catalysts. Suitable solvents are, for example, methanol, ethanol and the like. Amino groups may be alkylated or acylated following art-known procedures such as, for example, N-alkylation, N-acylation, reductive N-alkylation and the like methods.
- 25 The compounds of formula (I) containing an amino group substituted with a radical arylmethyl, may be hydrogenolyzed by treating the starting compound with hydrogen in the presence of a suitable catalyst, e.g., palladium-on-charcoal, platinum-on-charcoal and the like, preferably in an alcoholic medium. The compounds of formula (I) wherein L is methyl or phenylmethyl can be converted into compounds of formula (I) wherein L
- 30 is a C₁-alkyloxycarbonyl group by reacting the methyl or phenylmethyl derivative with C₁-alkyloxycarbonyl halides such as, for example, ethyl chloroformate in a suitable reaction-inert solvent and in the presence of a base like N,N-diethylethanamine. The compounds of formula (I) wherein L is hydrogen can be obtained from compounds of formula (I) wherein L is phenylmethyl or C₁-alkyloxycarbonyl following art-know

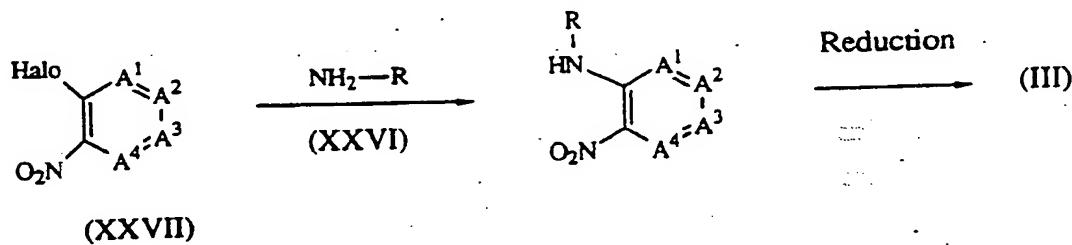
procedures like catalytic hydrogenation or hydrolysis in an acidic or alkaline medium depending on the nature of L.

- In all of the foregoing and in the following preparations, the reaction products may
5 be isolated from the reaction mixture and, if necessary, further purified according to
methodologies generally known in the art.

- Some intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds and others are new. A number of such preparation methods will be described hereinafter in more detail.

- Starting materials such as the intermediates of formulae (II), (IV), (VI), (VIII), (X), (XII), (XIII) and (XV) can conveniently be prepared following procedures similar to those described in for example, US-4,219,559; 4,556,660; 4,634,704; 4,695,569; 4,695,575, 4,588,722, 4,835,161 and 4,897,401 and in EP-A-0,206,415; 0,282,133; 0,297,661 and 0,307,014.

- The intermediates of formula (III) can be prepared from an aromatic starting material with vicinal halo and nitro substituents (XXVII) by reaction with a suitable amine of formula (XXVI), followed by art-known nitro-to-amine reduction.



- 25 The intermediates of formulae (V), (VII), (IX) and (XI) then, can be prepared from the intermediates of formula (III) following art-known procedures of converting aromatic products with vicinal amino groups into benzimidazoles, imidazopyridines and/or purines.

- 30 The compounds of formula (I), the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof possess useful pharmacological properties. More particularly, they are active antiallergic and antihistaminic compounds which activity can be demonstrated by, e.g., the results obtained in the test "Protection of Rats

from Compound 48/80-induced lethality", the "PCA (passive cutane anaphylaxis)-test in Rats" described in Drug Dev. Res., 5, 137-145 (1985), the "Histamine-induced lethality test in Guinea Pigs" and the "Ascaris Allergy test in Dogs". The latter two tests are described in Arch. Int. Pharmacodyn. Ther. 251, 39-51 (1981).

5

An interesting feature of the present compounds resides in their rapid onset of action and favorable duration of action.

In view of their antiallergic properties, the compounds of formula (I) and their acid 10 addition salts are very useful in the treatment of broad range of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria, allergic asthma and the like.

In view of their useful antiallergic properties the subject compounds may be 15 formulated into various pharmaceutical forms for administration purposes. To prepare the antiallergic compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. 20 These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, 25 elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise 30 sterile water, at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions 35 suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a

5 significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

20 The present invention also relates to a method of treating warm-blooded animals suffering from said allergic diseases by administering to said warm-blooded animals an effective antiallergic amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt form thereof.

Those of skill in treating allergic diseases in warm-blooded animals could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective antiallergic amount would be from about 0.001 mg/kg to about 20 mg/kg body weight, and more preferably from about 0.01 mg/kg to about 25 5 mg/kg body weight.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects. Unless otherwise stated all parts therein are by weight.

30 Experimental part

A. Preparation of the intermediates

Example 1

To a mixture of 15.5 parts of 2-chloro-1H-benzimidazole and 235 parts of N,N-di-methylacetamide there were added 22 parts of 4-(chloromethyl)-2-methylthiazole monohydrochloride and 25.4 parts of sodium carbonate. The whole was stirred for 18 hours at 75°C and was then poured into water. The product was extracted with

4-methyl-2-pentanone and the extract was washed with water, dried, filtered and evaporated. The residue was crystallized from 2,2'-oxybispropane, yielding 11.3 parts (42.8%) of 2-chloro-1-[(2-methyl-4-thiazoly)methyl]-1H-benzimidazole (interm. 1). In a similar manner there was also prepared 2-chloro-1-[(6-methyl-2-pyridinyl)methyl]-5 1H-benzimidazole (interm. 2).

Example 2

- a) To a stirred and refluxing mixture of 60 parts of 4-fluorobenzenethiol, 93 parts of 1-bromo-3-chloropropane, 100 parts of ethanol and 45 parts of water there was added 10 dropwise a solution of 19 parts of sodium hydroxide in 80 parts of water. Stirring at reflux temperature was continued for 8 hours. After cooling, the organic layer was separated and distilled under reduced pressure (1.7 10³ Pa), yielding two fractions of resp. 53 parts (bp. 136-140°C) and 32 parts (bp. 140-152°C) of product. Total yield : 85 parts of 1-[(3-chloropropyl)thio]-4-fluorobenzene (interm. 3).
- b) A mixture of 67.5 parts of intermediate 3; 42.9 parts of 1,4-dioxa-8-azaspiro[4,5]-decane, 47.7 parts of sodium carbonate, a few crystals of potassium iodide and 2400 parts of 4-methyl-2-pentanone was stirred for 70 hours at reflux temperature. The reaction mixture was filtered while hot and the filtrate was washed with 1,1'-oxybis-ethane and evaporated. The residue was triturated in 2,2'-oxybispropane while cooling 20 at -20°C. A first fraction of 4.4 parts of product was obtained by filtration. Evaporation of the mother liquor yielded a second fraction of 97 parts of product. Total yield : 101.4 parts of 1,4-dioxa-8-[3-[(4-fluorophenyl)thio]propyl]-8-azaspiro[4,5]decane; mp. 135.5-140°C (interm. 4)

25 Example 3

- a) A mixture of 2.44 parts of 6-methyl-2-pyridinemethanamine, 3.2 parts of 2-chloro-3-nitropyridine, 1.7 parts of sodium hydrogen carbonate and 120 parts of ethanol was stirred for 3 hours at reflux temperature. The reaction mixture was filtered while hot over diatomaceous earth. After cooling, the precipitate which formed in the filtrate was 30 filtered off and dried, yielding 2.5 parts (51%) of 6-methyl-N-(3-nitro-2-pyridinyl)-2-pyridinemethanamine; mp. 131.7°C (interm. 5).
- b) A mixture of 55 parts of intermediate 5; 2 parts of a solution of thiophene in methanol 4% and 480 parts of methanol was hydrogenated at normal pressure and at 50°C with 3 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of 35 hydrogen was taken up, the catalyst was filtered off over diatomaceous earth and the filtrate was evaporated, yielding 47 parts (99.7%) of N²-[(6-methyl-2-pyridinyl)methyl]-2,3-pyridinediamine (interm. 6).

- c) A mixture of 47 parts of ethyl 4-isothiocyanato-1-piperidinecarboxylate, 47 parts of intermediate 6 and 900 parts of tetrahydrofuran was stirred overnight at room temperature. There was added 2,2'-oxybispropane to enhance crystallization. The product was filtered off and dried, yielding 78.5 parts (83.5%) of ethyl 4-[[[2-[(6-methyl-2-pyridinyl)methyl]amino]-3-pyridinyl]amino]thioxomethyl]amino]-1-piperidinecarboxylate; mp. 176°C (interm. 7).

B. Preparation of the final compounds

Example 4

- 10 To a stirred mixture of 45 parts of 2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-benzimidazole and 376 parts of N,N-dimethylformamide there were added portionwise 12.2 parts of a dispersion of sodium hydride in mineral oil (60%) and, after stirring for 1/2 hour, a solution of 28 parts of 2-(chloromethyl)-6-methylpyridine monohydrochloride in some N,N-dimethylformamide. Stirring at room temperature was continued overnight. After the addition of ethanol, the reaction mixture was poured into water. The product was extracted with methylbenzene and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH₂Cl₂ / CH₃OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the ethanedioate (1:5/2) salt in acetonitrile. The product was filtered off and dried, yielding 27.8 parts (29.2%) of 1-[(6-methyl-2-pyridinyl)methyl]-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-benzimidazole ethanedioate (1:5/2); mp. 155.3°C (comp. 48).

Example 5

- 25 To a stirred mixture of 36.7 parts of compound 48 and 267 parts of tetrahydrofuran there were added 15.68 parts of ethyl chloroformate. Stirring was continued for 6 hours and then there were added 11.7 parts of N,N-diethylethanamine. After stirring over weekend, the reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH₂Cl₂ / CH₃OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 15.65 parts (44.3%) of ethyl 4-[[1-[(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-yl]-methyl]-1-piperidinecarboxylate; mp. 159.7°C (comp. 53).

Example 6

A mixture of 2.9 parts of ethyl 4-[(1H-benzimidazol-2-yl)amino]-1-piperidinecarboxylate, 1.8 parts of 4-(chloromethyl)-2-methylthiazole monohydrochloride, 2.12 parts of sodium carbonate and 45 parts of N,N-dimethylacetamide was stirred overnight at 70°C.

- 5 The reaction mixture was poured into water and the product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 1.5 parts (37.5%) of ethyl 4-[(1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazol-2-yl)amino]-1-piperidinecarboxylate; mp. 160°C (comp. 12).

10

Example 7

- A mixture of 25 parts of compound 12; 34 parts of potassium hydroxide and 160 parts of 2-propanol was stirred overnight at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was converted into the trihydrochloride salt in 2-propanol. The product was filtered off and dried, yielding 20 parts (71.2%) of 1-[(2-methyl-4-thiazolyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine trihydrochloride hemihydrate; mp. 206.4°C (comp. 13).

20 Example 8

- A mixture of 15 parts of compound 58 and 224 parts of hydrobromic acid 48% was refluxed for 3 hours. The reaction mixture was evaporated and the residue was taken up in water. After basifying with sodium hydroxide solution, the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was crystallized from acetonitrile, yielding 5 parts (41.3%) of 1-[(4-methyl-2-thiazolyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine (comp. 59).

Example 9

- A mixture of 2.3 parts of 6-(2-chloroethyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one, 3.3 parts of compound 13; 1.6 parts of sodium carbonate and 160 parts of 4-methyl-2-pentanone was stirred for 48 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel : CH₂Cl₂ / CH₃OH(NH₃) 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 1.64 parts (31.6%) of

7-methyl-6-[2-[4-[[1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-5H-thiazolo[3,2-a]pyrimidin-5-one; mp. 129.8°C (comp. 18).

Example 10

- 5 A mixture of 2.26 parts of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 3.2 parts of compound 2; 1.06 parts of sodium carbonate and 45 parts of N,N-dimethylacetamide was stirred overnight at 70°C. The reaction mixture was poured into water. The precipitate was filtered off and boiled in methanol. The product was filtered off while hot, yielding 2.1 parts (41.5%) of 2-methyl-3-[2-[4-[[3-[(6-methyl-2-pyridinyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidinyl]ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one; mp. 233.1°C (comp. 7).

Example 11

- 15 The following reaction was carried out under a nitrogen atmosphere. To a mixture of 7.5 parts of ethyl 4-hydroxy-1-piperidinecarboxylate and 94 parts of N,N-dimethylformamide there were added portionwise 2.1 parts of a dispersion of sodium hydride in mineral oil (50%). After stirring for 1 hour at room temperature and for 20 min at 40°C, there was added dropwise a solution of 11.3 parts of intermediate 1 in 94 parts of N,N-dimethylformamide. Stirring was continued overnight at room temperature. After 20 addition of some ethanol, the reaction mixture was evaporated. The residue was poured into ice-water and the whole was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH₂Cl₂ / CH₃OH 90:10). The eluent of the desired fraction was evaporated, yielding 13 parts (75.5%) of ethyl 4-[[1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazol-2-yl]-oxy]-1-piperidinecarboxylate (comp. 20).

Example 12

- 30 A mixture of 4.5 parts of compound 13; 2 parts of polyoxymethylene, 5 parts of potassium acetate and 120 parts of methanol was hydrogenated at normal pressure and at 50°C with 1 part of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off over diatomaceous earth. The filtrate was evaporated and the residue was taken up in water. After basifying with sodium carbonate, the product was extracted with trichloromethane. The extract was dried, filtered and evaporated and the residue was converted into the ethanedioate (1:2) salt in methanol. The product was filtered off and dried, yielding 3.7 parts (70.9%) of N-(1-methyl-4-piperidinyl)-1-[(2-methyl-4-thiazolyl)methyl]-1H-benzimidazol-2-amine ethanedioate (1:2); mp. 221.3°C (comp. 16).

Example 13

A mixture of 78 parts of intermediate 7; 58.5 parts of mercury(II)oxide, 1 part of sulfur and 800 parts of ethanol was stirred for 2 hours at reflux temperature. The reaction
5 mixture was filtered over diatomaceous earth and the filtrate was evaporated, yielding 63.5 parts (88.5%) of ethyl 4-[(3-[(6-methyl-2-pyridinyl)methyl]-3H-imidazo[4,5-b]-pyridin-2-yl]amino)-1-piperidinecarboxylate (comp. 1).

Example 14

10 Through a stirred mixture of 3.23 parts of compound 2 and 80 parts of methanol there were bubbled 0.9 parts of oxirane. Stirring was continued overnight at room temperature. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel ; CHCl₃ / CH₃OH 96:4). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered
15 off and dried, yielding 0.7 parts (19%) of 4-[(3-[(6-methyl-2-pyridinyl)methyl]-3H-imidazo[4,5-b]-pyridin-2-yl]amino)-1-piperidineethanol; mp. 152.0°C (comp. 4).

Example 15

20 A mixture of 9 parts of compound 5; 11 parts of potassium hydroxide and 120 parts of 2-propanol was stirred for 4 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane (2x) and the combined extracts were dried, filtered and evaporated, yielding 7.5 parts (100%) of N-[1-(2-aminoethyl)-4-piperidinyl]-3-[(6-methyl-2-pyridinyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine (comp. 8).

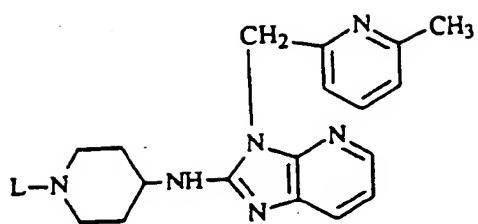
25

Example 16

30 A mixture of 1.2 parts of 2-chloropyrimidine, 3.7 parts of compound 8; 0.9 parts of sodium hydrogen carbonate and 80 parts of ethanol was stirred overnight at reflux temperature. The reaction mixture was filtered over diatomaceous earth and the filtrate was evaporated. The residue was crystallized from a mixture of acetonitrile and methanol. The product was filtered off and dried in vacuo at 130°C overnight, yielding 1 part (22.5%) of 3-[(6-methyl-2-pyridinyl)methyl]-N-[1-[2-[(2-pyrimidinyl)amino]-ethyl]-4-piperidinyl]-3H-imidazo[4,5-b]pyridin-2-amine; mp. 187.4°C (comp. 9).

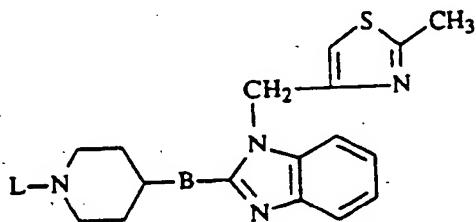
35 All compounds listed in tables 1, 2, 3, 4 and 5 were prepared following methods of preparation described in examples 4 - 16, as is indicated in column 2 (Ex. No.)

28

Table 1

Comp. No.	Ex. No.	L	Physical data
1	13	CH ₃ -CH ₂ -OOC-	
2	7	H-	147.6°C / H ₂ O(1:1/2)
3	12	CH ₃ -	130.5°C
4	14	HO-(CH ₂) ₂ -	152.0°C
5	10	CH ₃ -CH ₂ -OOC-NH-(CH ₂) ₂ -	139.6°C
6	10	CH ₃ O-C ₆ H ₄ -(CH ₂) ₂ -	142.3°C
7	10		233.1°C
8	15	NH ₂ -CH ₂ -CH ₂ -	-
9	16		187.4°C
10	9		185.4°C
11	9		215.5°C

5

Table 2

Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
12	6	CH ₃ -CH ₂ -OOC-	NH	160°C
13	7	H	NH	206.4°C/HCl (1:3)/H ₂ O (1:1/2)
14	10	CH ₃ -CH ₂ -O-(CH ₂) ₂ -	NH	201.6°C/(COOH) ₂ (1:2)
15	10	CH ₃ O-C ₆ H ₄ -(CH ₂) ₂ -	NH	228.5°C/HCl (1:2)/H ₂ O
16	12	CH ₃ -	NH	221.3°C/(COOH) ₂ (1:2)
17	9		NH	185.4°C
18	9		NH	129.8°C
19	9		NH	186.1°C
20	11	CH ₃ -CH ₂ -OOC-	O	-
21	7	H	O	127.7°C
22	9		O	137.0°C
23	9		O	160.4°C
24	4	C ₆ H ₅ -CH ₂ -	CH ₂	115.1°C
25	5	CH ₃ -CH ₂ -OOC-	CH ₂	125.0°C
26	7	H	CH ₂	155.9°C
27	9		CH ₂	150.7°C (E)-2-butenedioate (1:3/2) 2-propanolate(1:1)
28	9		CH ₂	153.4°C

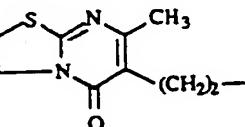
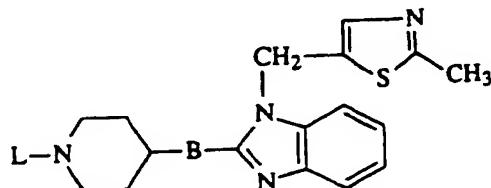
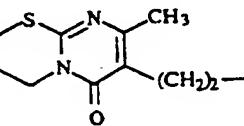
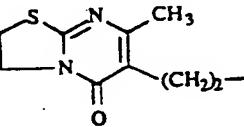
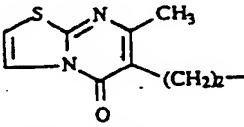
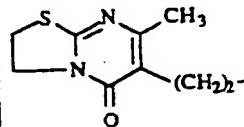
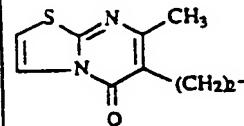
Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
29	9		CH ₂	179.9°C

Table 3



Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
30	6	CH ₃ -CH ₂ -OOC-	NH	155.1°C
31	7	H-	NH	239.2°C
32	9		NH	196.7°C
33	9		NH	204.2°C
34	9		NH	125.5°C
35	4	C ₆ H ₅ -CH ₂ -	CH ₂	119.6°C
36	5	CH ₃ -CH ₂ -OOC-	CH ₂	101.3°C
37	7	H-	CH ₂	-
38	9		CH ₂	161.7°C / H ₂ O (1:1/2)
39	9		CH ₂	158.5°C / H ₂ O (1:3/2)

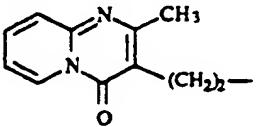
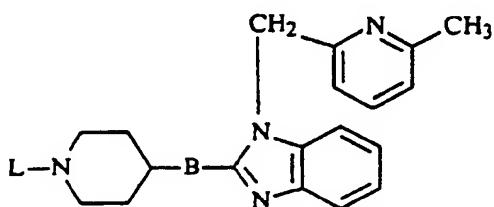
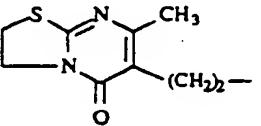
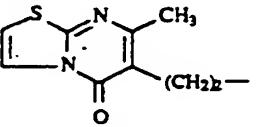
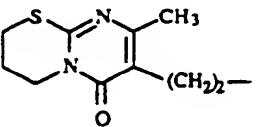
Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
40	9		CH ₂	171.0°C
41	9		NH	219.8°C
42	12	H ₃ C-	NH	114.6°C/H ₂ O (1:3/2)
43	9	CH ₃ O-C ₆ H ₄ -(CH ₂) ₂ -	NH	103.1°C

Table 4



Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
44	6	CH ₃ -CH ₂ -OOC-	NH	182.6°C
45	7	H	NH	161.0°C/H ₂ O (1:1/2)
46	9		NH	206.6°C
47	9		NH	225.3°C
48	4	C ₆ H ₅ -CH ₂ -	CH ₂	155.3°C/(COOH) ₂ (1:5/2)
49	9		NH	131.9°C / H ₂ O
50	11	CH ₃ -CH ₂ -OOC-	O	-
51	7	H	O	106.9°C

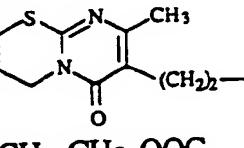
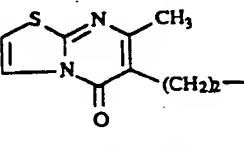
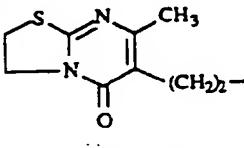
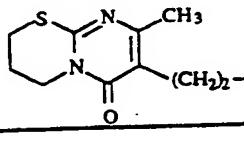
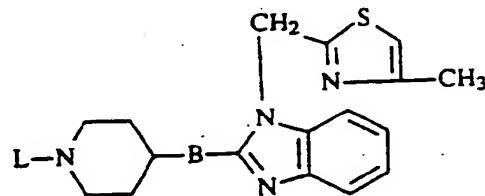
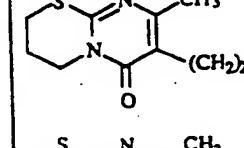
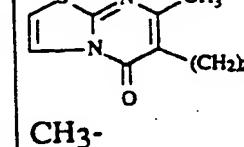
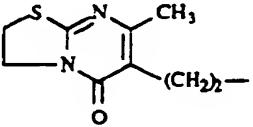
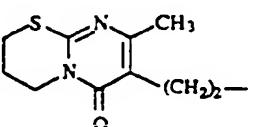
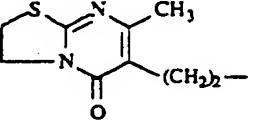
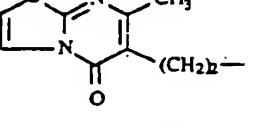
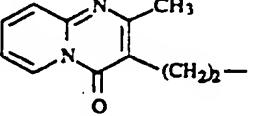
Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
52	9		O	144.0°C
53	5	CH ₃ -CH ₂ -OOC-	CH ₂	159.7°C
54	7	H	CH ₂	-
55	9		CH ₂	176.1°C
56	9		CH ₂	222.5°C (E)-2-butenedioate(1:1)
57	9		CH ₂	160.6°C (E)-2-butenedioate(1:3/2) 2-propanolate(1:1)

Table 5



Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
58	6	CH ₃ -CH ₂ -OOC-	NH	183.6°C
59	8	H-	NH	-
60	9		NH	147.7°C / H ₂ O
61	9		NH	215.5°C
62	12	CH ₃ -	NH	128.5°C/H ₂ O (1:1/2)

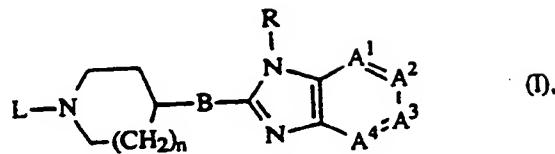
Comp. No.	Ex. No.	L	B	Physical data (mp. - salt)
63	9		NH	196.7°C
64	9	CH ₃ O-C ₆ H ₄ -(CH ₂) ₂ -	NH	109.9°C
65	4	C ₆ H ₅ -CH ₂ -	CH ₂	129.5°C
66	5	CH ₃ -CH ₂ -OOC-	CH ₂	-
67	7	H-	CH ₂	-
68	9		CH ₂	126.6°C
69	9		CH ₂	170.4°C
70	9		CH ₂	176.9°C (Z)-2-butenedioate(1:2)
71	9		CH ₂	158.8°C

C. Pharmacological example5 **Example 17**

The useful anti-allergic and anti-histaminic properties of the compounds of formula (I) can be demonstrated, e.g., in the test "Protection of rats from compound 48/80-induced lethality" which is described in US-4,556,660. The compounds of formula (I) were administered subcutaneously and/or orally to rats. The ED₅₀-value (mg/kg) for the 10 compounds 9, 16, 19, 23, 27, 28, 29, 55, 62, 69 and 70 was found to be 0.04 mg/kg.

Claims

1. A compound having the formula :



5

a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

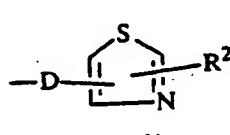
10 $-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula

- CH=CH-CH=CH- (a-1),
- N=CH-CH=CH- (a-2),
- CH=N-CH=CH- (a-3),
- CH=CH-N=CH- (a-4),
- CH=CH-CH=N- (a-5),
- N=CH-N=CH- (a-6) or
- CH=N-CH=N- (a-7);

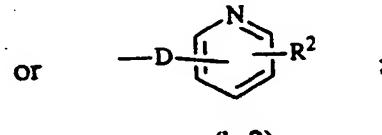
15

20 wherein one or two hydrogen atoms in said radicals (a-1) to (a-7) may each independently be replaced by halo, C₁-6alkyl, C₁-6alkyloxy, hydroxy or trifluoromethyl;

B represents NR¹, CH₂, O, S, SO or SO₂ wherein R¹ is hydrogen or C₁-4alkyl;
25 R is a radical of formula;



(b-1)



(b-2)

30 wherein D is C₁-4alkanediyl;
R² is C₁-6alkyl;
n is 0, 1 or 2;
L is hydrogen; C₁-12alkyl; C₃-6cycloalkyl; C₃-6alkenyl optionally substituted with aryl; C₁-6alkylcarbonyl; C₁-6alkyloxycarbonyl; arylcarbonyl; arylC₁-6alkyloxy-carbonyl; or a radical of formula

35

35

- Alk-R³ (c-1);
- Alk-Y-R⁴ (c-2);
- Alk-Z¹-C(=X)-Z²-R⁵ (c-3); or
- CH₂-CHOH-CH₂-O-R⁶ (c-4); wherein

5

- R³ is cyano, aryl or Het;
- R⁴ is hydrogen, aryl, Het or C₁-alkyl optionally substituted with aryl or Het;
- R⁵ is hydrogen, aryl, Het or C₁-alkyl optionally substituted with aryl or Het;
- R⁶ is aryl or naphthalenyl;
- Y is O, S, NR⁷; said R⁷ being hydrogen, C₁-alkyl or C₁-alkylcarbonyl;
- Z¹ and Z² each independently are O, S, NR⁸ or a direct bond; said R⁸ being hydrogen or C₁-alkyl;
- X is O, S or NR⁹; said R⁹ being hydrogen, C₁-alkyl or cyano;
- each Alk independently is C₁-alkanediyl;
- 15 each Het is :
- (i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms selected from oxygen, sulfur and nitrogen, provided that no more than 2 oxygen and/or sulfur atoms are present;
 - 20 (ii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring only carbon atoms; or
 - 25 (iii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered heterocyclic ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen;
- 30 wherein Het being a monocyclic ring system may be optionally substituted with up to 4 substituents; and wherein Het being a bicyclic ring system may be optionally substituted with up to 6 substituents, said substituents being selected from halo, amino, mono- and di(C₁-alkyl)amino, arylC₁-alkylamino, nitro, cyano, aminocarbonyl, C₁-alkyl, C₁-alkyloxy, C₁-alkylthio, C₁-alkyloxycarbonyl, C₁-alkyloxyC₁-alkyl,
- 35 C₁-alkyloxycarbonylC₁-alkyl, hydroxy, mercapto, hydroxyC₁-alkyl, C₁-alkyl-carbonyloxy, aryl, arylC₁-alkyl, carboxyl, C₁-alkylaminocarbonylamino, aryl-aminocarbonylamino, oxo or thio; and

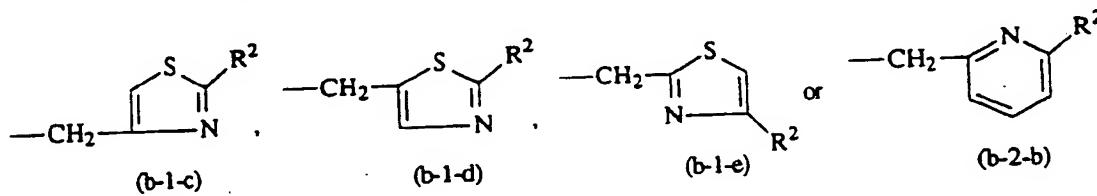
36

each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C₁-alkyl, C₁-alkyloxy, C₁-alkylthio, mercapto, amino, mono- and di(C₁-alkyl)amino, carboxyl, C₁-alkyloxycarbonyl and C₁-alkylcarbonyl.

5

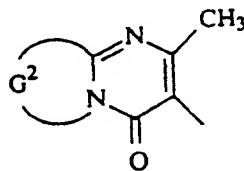
2. A compound according to claim 1 wherein -A¹=A²-A³=A⁴, represents a bivalent radical of formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2); B represents NH, CH₂ or O; R represents a radical of formula

10



15

R² represents C₁-4alkyl; n is 1; L represents hydrogen, C₁-4alkyl, C₁-4alkyloxy-carbonyl or a radical of formula -Alk-R³ (c-1), -Alk-Y-R⁴ (c-2) or -Alk-Z¹-C(=X)-Z²-R⁵ (c-3); Alk represents C₁-4alkanediyl; R³ represents phenyl, C₁-4alkyloxyphenyl or a radical of formula

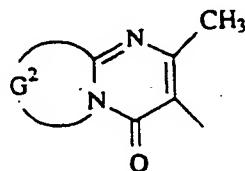


20

wherein G² represents -CH=CH-CH=CH-, -S-(CH₂)₃-, -S-(CH₂)₂- or -S-CH=CH-; Y represents O or NH; R⁴ represents hydrogen, C₁-4alkyl or pyrimidinyl; R⁵ represents C₁-4alkyl; Z¹ represents NH; Z² represents O; and X represents O.

25

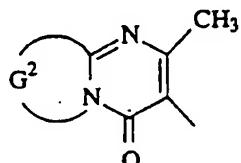
3. A compound according to claim 1 wherein B represents NH or CH₂; R² represents methyl; L represents C₁-4alkyl or a radical of formula -Alk-R³ (c-1), -Alk-Y-R⁴ (c-2) or -Alk-Z¹-C(=X)-Z²-R⁵ (c-3); Alk represents C₂-4alkanediyl; R³ represents 4-methoxyphenyl or a radical of formula



37

wherein G² represents -CH=CH-CH=CH-, -S-(CH₂)₃-; -S-(CH₂)₂-; -S-CH=CH-; Y represents O or NH; R⁴ represents C₁₋₄alkyl or 2-pyrimidinyl.

4. A compound according to claim 1 wherein L represents methyl or a radical of
5 formula -Alk-R³ (c-1), Alk represents 1,2-ethanediyl and R³ represents 4-methoxy-phenyl or a radical of formula



- 10 wherein G² represents CH=CH-CH=CH-, -S-(CH₂)₃- , -S-(CH₂)₂- or -S-CH=CH-.

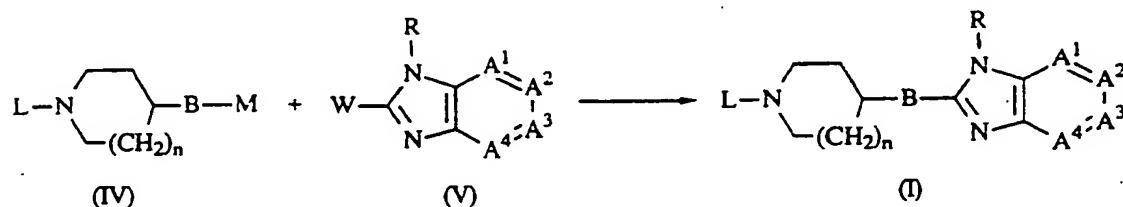
5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient an effective antiallergic amount of a compound as claimed in claim 1.

15 6. A process for preparing a pharmaceutical composition as claimed in claim 5, characterized in that a therapeutically effective amount of a compound as claimed in any of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.

7. A compound as claimed in any of claims 1 to 4 for use as a medicine.

20 8. A process of preparing a compound as claimed in claim 1, characterized by

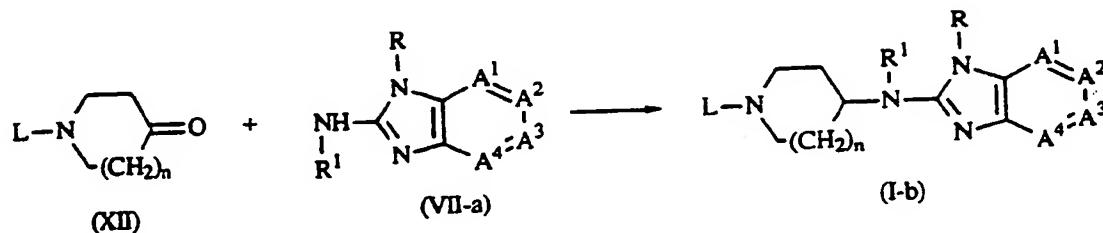
25 a) reacting a piperidine of formula (IV) wherein M represents hydrogen when B is other than hydrogen, or wherein M represents an alkali or earth alkaline metal when B represents CH₂, with a reagent of formula (V) wherein W represents a reactive leaving group,



- 30 in a reaction-inert solvent, optionally in the presence of a base;

38

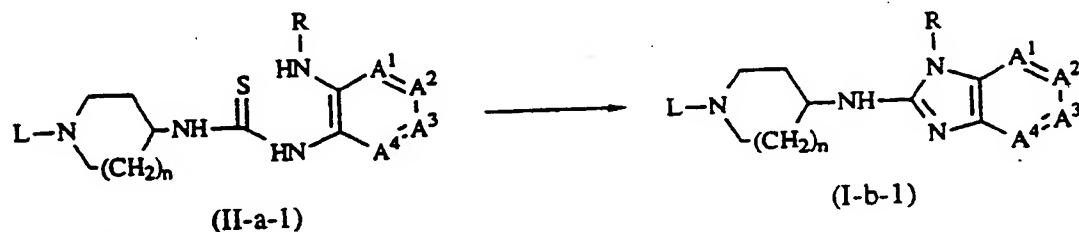
- b) reductively N -alkylating a 4-piperidinone derivative of formula (XII) with an amine of formula (VII-a),



5

in the presence of an appropriate reductant in a reaction-inert solvent, thus yielding a compound of formula (I-b);

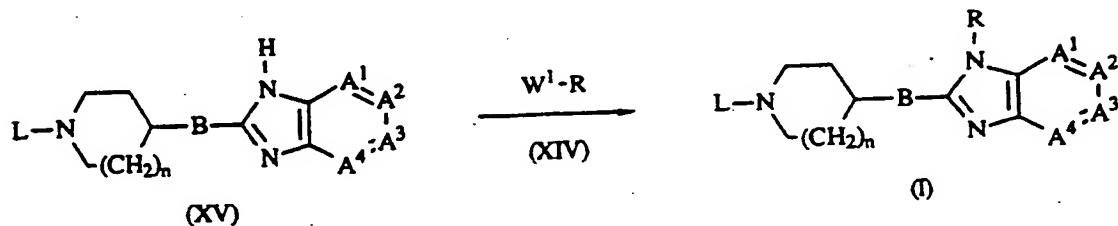
10



by reaction with a metal oxide or salt in a reaction-inert solvent, optionally in the presence of a small amount of sulfur;

15

- d) N -alkylating an intermediate of formula (XV) with an alkylating reagent of formula (XIV) wherein W represents a reactive leaving group,



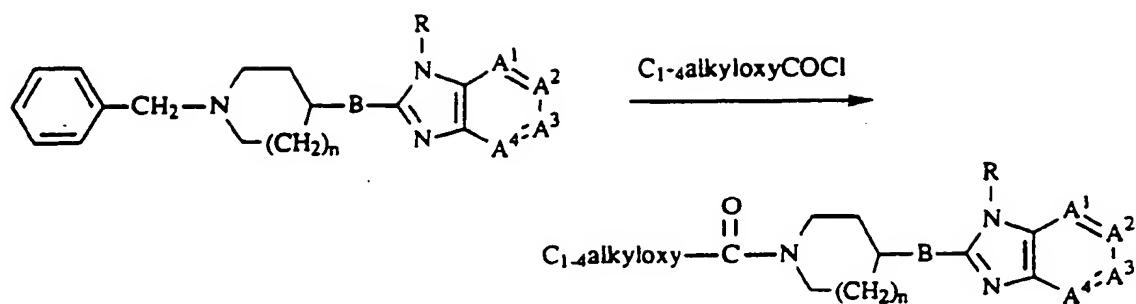
20

in a reaction-inert solvent in the presence of a base and at an elevated temperature;

- e) converting a compound of formula (I) wherein L represents benzyl into a compound wherein L represents $\text{C}_1\text{-4alkyloxycarbonyl}$,

25

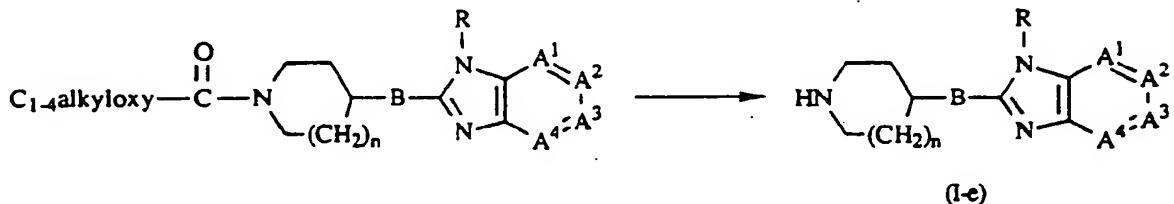
39



by reaction with a $\text{C}_1\text{-4alkylchloroformate}$ in the presence of a base in a reaction-inert solvent;

5

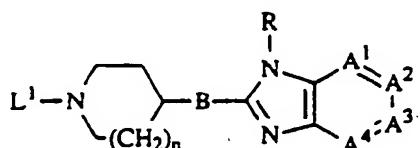
- f) hydrolyzing a compound of formula (I) wherein L represents $\text{C}_1\text{-4alkyloxy}$ -carbonyl in an aqueous acidic or basic medium to a compound of formula (I-e),



10.

- g) N -alkylating a compound of formula (I-e) with an alkylating reagent of formula $\text{L}^1\text{-W}^1$ (XVI) in a reaction-inert solvent in the presence of a base, thus preparing a compound of formula

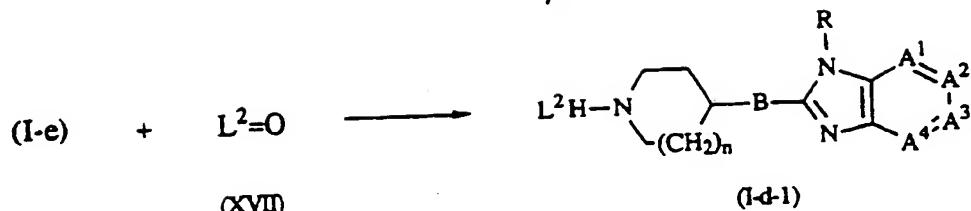
15



20

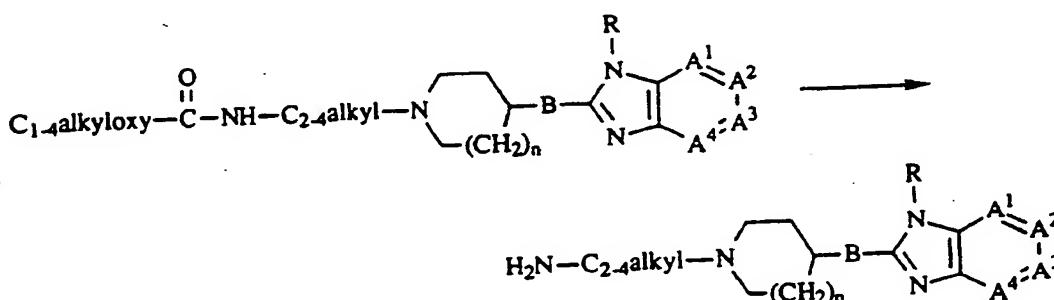
- h) reductively N -alkylating a compound of formula (I) with an aldehyde or ketone of formula $\text{L}^2=\text{O}$ (XVII) wherein L^2 represents a geminal bivalent radical comprising C_{3-6} cycloalkylidene, C_{1-12} alkylidene, $\text{R}^3\text{-C}_{1-6}$ alkylidene, $\text{R}^4\text{-Y-C}_{1-6}$ alkylidene or $\text{R}^5\text{-Z}^2\text{-C(=X)-Z}^1\text{-C}_{1-6}$ alkylidene,

40

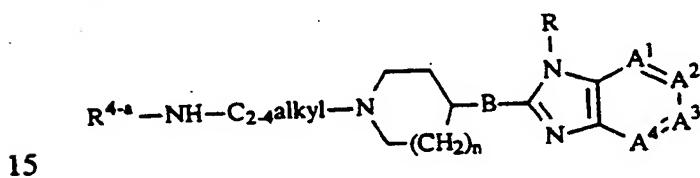


in a reaction-inert solvent in the presence of a reductant;

- 5 i) hydrolyzing a compound of formula (I) wherein L represents C_1 -4alkyloxy-carbonylaminoC₂-4alkyl in a basic aqueous medium thus yielding a compound wherein L represents an aminoC₂-4alkyl radical,

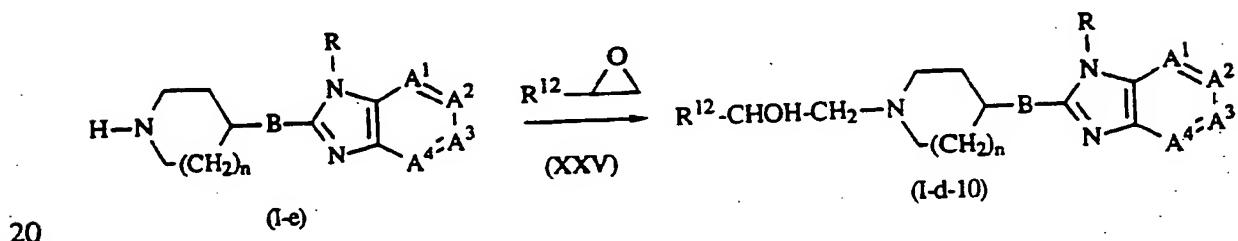


- 10 j) alkylating the thus obtained compound wherein L represents aminoC₂-4alkyl with a reagent of formula $R^{4-a}W^1$ wherein R^{4-a} represents aryl or Het and W^1 represents a reactive leaving group thus yielding a compound of formula



15

- k) reacting a compound of formula (I-e) with an epoxide of formula (XXV) wherein R^{12} represents hydrogen, C_1 -4alkyl or R^6-O-CH_2- ,



20

41

in a reaction-inert solvent; and, if desired, converting the compounds of formula (I) into a salt form by treatment with a pharmaceutically acceptable acid or conversely, converting the salt form into the free base by treatment with alkali; and/or preparing stereochemically isomeric forms thereof.

5

O

O

INTERNATIONAL SEARCH REPORT

International Appl. No. PCT/EP 91/01292

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶				
According to International Patent Classification (IPC) or to both National Classification and IPC				
Int.C1.5	C 07 D 513/04	C 07 D 401/14	C 07 D 401/04	
	C 07 D 519/00	C 07 D 473/40	A 61 K 31/505	A 61 K 31/425
	C 07 D 417/14, C 07 D 471/04, C 07 D 473/00,	C 07 D 473/30, A 61 K 31/52		
II. FIELDS SEARCHED				
Minimum Documentation Searched ⁷				
Classification System	Classification Symbols			
Int.C1.5	C 07 D	A 61 K		
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸				
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹				
Category ¹⁰	Citation of Document ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³		
X	EP,A,0297661 (JANSSEN PHARMACEUTICA NV) 4 January 1989, see the whole document (cited in the application) ---	1-8		
X	EP,A,0206415 (JANSSEN PHARMACEUTICA NV) 30 December 1986, see the whole document (cited in the application) ---	1-8		
X	US,A,4897401 (JANSSEN PHARMACEUTICA NV) 30 January 1990, see the whole document (cited in the application) ---	1-8		
X	US,A,4835161 (JANSSEN PHARMACEUTICA NV) 30 May 1989, see the whole document (cited in the application) ---	1-8		
<p>¹⁰ Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance. "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed</p> <p>¹¹ T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family</p>				
IV. CERTIFICATION				
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report			
07-10-1991	19 NOV 1991			
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer <i>[Signature]</i> Mme N. KUIPER			

III. DOCUMENTS CONSIDERED TO BE RELEVANT		(CONTINUED FROM THE SECOND SHEET)
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,4634704 (JANSSEN PHARMACEUTICA NV) 6 January 1987, see the whole document (cited in the application) ---	1-8
X	EP,A,4556660 (JANSSEN PHARMACEUTICA NV) 3 December 1985, see the whole document (cited in the application) ---	1-8
X	US,A,4588722 (JANSSEN PHARMACEUTICA NV) 13 May 1986, see the whole document (cited in the application) ---	1-8
X	US,A,4695569 (JANSSEN PHARMACEUTICA NV) 22 September 1987, see the whole document (cited in the application) ----	1-8
X	EP,A,4695575 (JANSSEN PHARMACEUTICA NV) 22 September 1987, see the whole document (cited in the application) -----	1-8

FURTHER INFORMATION C NTINUED FROM THE SECOND SHEET**V. OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹**

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim numbers * because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

* Claims searched incompletely: 1-8
As the drafting of the claims is not clear and concise (Art. 6 PCT) and encompasses such an enormous amount of products, a complete search is not possible on economic grounds (Art 17(2)(a)(ii), PCT). So the search has been based on the examples

3. Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple Inventions in this International application as follows:

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:
3. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.
 No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9101292
SA 49002

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 06/11/91.
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0297661	04-01-89	AU-B-	603684	22-11-90
		AU-A-	1835388	05-01-89
		JP-A-	1034979	06-02-89
		US-A-	4988689	29-01-91
EP-A- 0206415	30-12-86	AU-B-	588890	28-09-89
		AU-A-	5919186	08-01-87
		CA-A-	1267889	17-04-90
		JP-A-	62000487	06-01-87
		SU-A-	1581221	23-07-90
		US-A-	5041448	20-08-91
US-A- 4897401	30-01-90	US-A-	5006527	09-04-91
		AU-B-	600144	02-08-90
		AU-A-	1810988	22-12-88
		EP-A-	0295742	21-12-88
		JP-A-	1025776	27-01-89
		SU-A-	1644717	23-04-91
US-A- 4835161	30-05-89	AU-B-	583706	04-05-89
		AU-A-	6821887	06-08-87
		EP-A-	0232937	19-08-87
		JP-A-	62215575	22-09-87
US-A- 4634704	06-01-87	AU-B-	565884	01-10-87
		AU-A-	3387284	18-04-85
		CA-A-	1247614	27-12-88
		EP-A, B	0145037	19-06-85
		JP-A-	61010577	18-01-86
		SU-A-	1440346	23-11-88
EP-A- 4556660		None		
US-A- 4588722	13-05-86	AU-B-	575612	04-08-88
		AU-A-	3736385	01-08-85
		CA-A-	1246070	06-12-88
		EP-A, B	0151824	21-08-85
		SU-A-	1400509	30-05-88
		JP-A-	60174778	09-09-85

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9101292
SA 49002**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 06/11/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4695569	22-09-87	AU-B-	579121	17-11-88
		AU-A-	3602884	06-06-85
		CA-A-	1257258	11-07-89
		EP-A, B	0144101	12-06-85
		JP-A-	60149583	07-08-85
		SU-A-	1500162	07-08-89
		US-A-	4888426	19-12-89
		US-A-	5025014	18-06-91
EP-A- 4695575		None		